Hepatocellular Adenomas: Genetics & Imaging Update 2017

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Aims & Objectives

- To provide a current update on genetics & molecular biology of hepatocellular adenomas
- To correlate imaging findings with genotype-phenotype tumor features
- Discuss implications on management
Monoclonal, hepatocellular neoplasms typically described in young women on oral contraceptives
- Increased proclivity to bleed & rupture
- Rare malignant transformation
- Serial surveillance or surgical resection

Epidemiology and Pathology of HCA

- Incidence in 1970’s: 3–4/100,000 in OC pill users.
- Hormone dependent tumor
  - Occur predominantly in young women (M:F-1:10; Mean age– 41 yrs)
  - >90% women with HCA have h/o OC pill use; Relative Risk:1.25-2.8.
  - Grow in pregnancy and regress with cessation of OC use
- Other risk factors:- Anabolic steroid intake, Glycogen storage disorder (Ia, III, IV, VI), Tyrosinemia, Galactosemia, Steatohepatitis, Hemochromatosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Steatotic HCA (35-50%)</th>
<th>Inflammatory HCA (40-55%)</th>
<th>β-catelin mutated HCA (10-18%)</th>
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<tbody>
<tr>
<td><strong>‘Hallmark’ histology</strong></td>
<td>Marked steatosis</td>
<td>Marked peliosis, polymorphous inflammatory infiltrates, thick tortuous arteries</td>
<td>Cholestasis No significant peliosis or steatosis</td>
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<td><strong>Immunostaining</strong></td>
<td>Lack of expression of Liver Fatty Acid Binding Protein (LFABP)</td>
<td>Strong expression of serum amyloid associated protein A2 (SAA-2) and CRP</td>
<td>Strong, diffuse, over-expression of glutamine synthetase &amp; nuclear β-catelin staining</td>
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Pathogenesis of HCA: A tale of 3 major pathways

- **Inflammatory HCA**
  - Activation of Jak-Stat pathway
  - HNF-1α gene mutation

- **Steatotic HCA**
  - Good

- **Malignant HCA**
  - β-catenin gene mutation
  - Ugly

Biomarkers: Hepatocellular adenomas

Inflammatory HCA

Steatotic HCA

FNH

β-catenin mutated HCA

Pathogenesis of HCA: Inflammatory HCA

**Interleukin 6 pathway**

- **Interleukin 6**
  - gp130
  - IL6Ra
  - IL6Ra
  - gp130

- **JAK1**
  - STAT1/3
  - STAT3

- **JAK2**

**Interferon pathway**

- **IFN α/β**
  - IFNAR1
  - IFNAR2
  - IFNGR1
  - IFNGR2

- **IFN γ**
  - IFNAR1
  - IFNAR2
  - IFNGR1
  - IFNGR2

- **TYK2**
  - JAK1
  - JAK1
  - JAK2

- **STAT1/2**
  - STAT1

- **ISGF3G**
  - ISGF
  - STAT1/2

- **Sustained activation of JAK-STAT pathway**

**Overexpression of chemokine CCL20**

- Chemoattractant for B, T, & dendritic cells

**Inflammatory HCA**

- Polymorphous inflammatory infiltrates
- Hepatocellular proliferation
- Marked peliosis
- Suppression of ALB, IGF1, TTR

Inflammatory HCA

Increased lipogenesis

HNF-1α mutation

Down-regulation of FABP1 (Fatty acid binding protein) results in ‘faulty’ transport of fatty acids

Accumulation of intracellular fat

Increased lipogenesis

Cellular proliferation

Suppression of gluconeogenesis

Activation of glycolysis

Promotion of fatty acid biosynthesis

Somatic or Genetic HNF-1α gene Mutation

Suppression of estradiol detoxification

Diffuse tumoral steatosis

Hepatocellular proliferation

Steatotic HCA

Angiogenesis

ErbB2

PI3K

PDGFA

PDGFB

AKT

mTOR

Bacq et al. Gastroenterology 2003; 125:1470-1475
β-catenin pathway - 20-30%

Normal

β-catenin pathway is characterized by rapid degradation of β-catenin, which prevents its uncontrolled action. This results in normal cellular processes such as differentiation, zonation, proliferation, and regeneration of hepatocytes.

Mutation

In the mutated state, β-catenin activation leads to sustained uncontrolled proliferation and tumor formation. This pathway is associated with gain of oncogenes and loss of anti-oncogenes, typically seen in HCA and HCC in Glycogen Storage Disease.

Other pathways

Gain of Oncogenes: Chromosome 6p

Loss of Anti-Oncogenes: IGF2R and LATS1

Symptomatic patient (Rupture / Bleeding)

- Hemodynamically stable
  - Surgical resection
  - RFA?

- Hemodynamically unstable
  - Transcatheter Embolization
Asymptomatic HCA: Management

HCA’s in men, GSD, >5 cm, complications, β-catenin mutations → Resect

Fatty HCA’s <5 cm → Stop offending drug Surveillance

Genotype-phenotype classification: a paradigm shift in imaging and management of HCA

Imaging plays a key role in the diagnosis & characterization of HCAs as well as in surveillance following management.

HCAs with HNF-1α gene mutations are diffusely steatotic, never undergo malignant transformation & are associated with familial diabetes (MODY 3)/familial adenomatosis.
Inflammatory HCAs tend to bleed & are associated with obesity, alcohol use and steatosis.

Inflammatory HCAs may present with inflammatory syndrome with elevated markers.

HCAs with β-catenin mutations are seen with male hormone intake and glycogen storage disease, frequently undergo malignant change and may mimic HCC on imaging.
Steatotic HCAs can be monitored by imaging.

HCAs associated with metabolic syndrome, GSD & HCAs in males warrant biopsy/surgery.

All HCAs more than 5 cm require biopsy/surgery.

Hepatic adenomatoses, by itself is not an independent risk factor for complications.

HCAs in young women and in pregnancy may need more aggressive approach.